isms. In so doing, man, the conscious organism, would assume a dominating rôle in the world of organisms and create relations among living things not now existent.

D. T. MACDOUGAL

TENDENCIES IN PATHOLOGY[1]

DURING the first half of the nineteenth century the science of pathological anatomy was created. Its rise was part of the development in the natural sciences which marked the beginnings of the intellectual expansion of the century, and its growth has continued unbroken up to the present day. Out of the science of anatomical pathology, which stands as the foundation subject of those disturbances in structure and function that constitute disease, there arose other sciences the pursuit of which has served to increase our understanding of the nature of disease. Chief among these are the sciences of general pathology, erected on the foundation laid by the discoveries in physiology, of pathological chemistry, which has grown out of the study by physiologists of the chemical changes connected with the different organic functions, and of the discovery by organic chemists of the nature and constitution of the compounds composing the organic skeleton and produced in the course of organic metabolism, and of bacteriology, that quickening subject, emerging Minerva-like out of the epochal investigations of spontaneous generation and the biology of microscopic plants and animals, which gave to medicine in a few pregnant years an era of discovery in the domain of the causation and the specific treatment of disease unparalleled in all medical history. The resultant of the discoveries in the newer fields of pathological knowledge constitutes the period of etiological pathology which, dating its beginnings from the middle of the last century, is to-day the dominant influence affecting medical thought. It is my wish to present to you briefly, as can only be done in the limits of a short address, certain of the tendencies in the study of pathology to be discovered at the present time.

To compass this broad field superficially even would demand more of your time than would be permissible on this occasion, so great are the activities to-day with which the subjects of general pathology, biological chemistry and bacteriology are being pursued. I have, therefore, adopted a very arbitrary course in the choice of subject-matter to bring before your attention and I have chosen to allude briefly to certain fields of inquiry in general pathology and to deal somewhat more fully with certain newer problems in bacteriology which are commanding at the moment the attention of the best laboratories, and I have left the fascinating field of biological chemistry to be dealt with by a far abler hand than mine.

The causation of disease is manifold, the reaction to abnormal influences is varied. The forces which divert the normal functions and bring disease into being are only in part external, at the time of their operation, to the body. All parasitic plants and animals, which disturb function or alter structure and produce disease, are essentially extrinsic agents of injury and have been introduced from without either during intrauterine life, of which there now exists objective proofs, or later in the period of post-fetal existence. The many causes of occupation diseases, so-called, in which we recognize the introduction into the body chiefly with the inspired air, but also by way of the digestive tract and possibly by way of other mucous surfaces and the skin, of injurious foreign particles, are at present only slightly understood and act not wholly,

[1] Address of the vice-president and chairman of Section K, Physiology and Experimental Medicine, American Association for the Advancement of Science, Chicago meeting, 1907.

probably, by increasing susceptibility to bacterial and allied infections, but often through direct chemical and physical malinfluences. A wide-spread interest in the improvement of the physical condition of the race, which has grown out of the social propaganda for bettering the condition of the poor, has produced in many quarters an active inquiry into the pathology of the occupation diseases from which much enlightenment may be confidently expected. But a complete knowledge of these external agencies, when it shall have been acquired, will probably fail to secure to us a full knowledge of the conditions which underlie all disease, since there is a class of diseases, some of very subtile nature, apparently, which result, in part at least, from errors and disturbances of balance in the development of the animal organism or in the correlation of its functions, of which we are at present beginning to appreciate the significance. The remarkable chain of events through which the function of one organ or set of tissues is determined and controlled by the secretion of another organ or set of tissues, as is displayed in the influence of excessive or diminished thyroid secretion on the state of nutrition of the body and functions of its important viscera, and of the metabolic products of fetal tissues upon the hypertrophy and growth and function of the mammary gland, can serve to indicate how dependent is progress in pathology upon knowledge of physiology and chemistry.

Physiology, pathological anatomy and experimental pathology having each contributed a share which the others could not have supplied, are promising to solve some of the problems of arterial hypertension and arterial degeneration in Bright's disease. The peculiar control which the adrenals exercise over the tone of the vascular system can be altered in two ways so as either to depress and relax the circulation or to exalt and increase its tension. The first, a result of ablation or tubercular disease, as in Addison's disease, is clearly of extrinsic origin; but the second, which is associated with certain changes in the gland of an adenomatous character, may not be so. It is this latter condition which has now been found a number of times in cases of sclerosis and atrophy of the kidneys associated with arterial hypertension and degeneration. Recalling the effects of adrenalin in increasing blood pressure, of the degenerations of the aorta produced in rabbits by injections of this drug, and the clinical phenomena in this class of cases of Bright's disease, it seems a natural step to associate the adrenal, the nephritic and arterial disease into one pathological complex. Whether the primary pathological condition is to be discovered in the kidneys and the histological alterations in the adrenals are consequent upon this, as the arterial degenerations are viewed as secondary to the changes in the adrenal, or the order is to be reversed, in which case the changes in the kidneys are to be conceived as following upon those in the arterial system, can only be surmised at the present time. But we may still view this tangible basis of observation and possibly of experiment with hope that in it somewhere may be found the key to the understanding of this complex and vastly important chapter of pathology.

Examples showing the importance of glandular integrity in maintaining a state of health and of disintegrity in producing diseases could, with our present knowledge, be multiplied so as to include most of the glandular organs. Many of these examples would be familiar to you. In some of the best understood examples the number of possible alterations in the glands is two, at least, and the pathological effects are different according as the secretion is

diminished or increased in quantity. A notable instance of this kind is found in the relation of the thyroid gland to myxœdema and to Basedow's disease. Still another instance, possibly, has just been mentioned in connection with the adrenal gland. But in the pancreas it seems not improbable that one and the same pathological effect is or can be produced by changes in the islands of Langerhans which make for diminution of secretion, or its increase, with, in the latter case, possibly, a qualitative change in its chemical composition. That is to say, atrophy and degeneration of the islands have now been found so many times in the pancreas of persons succumbing to diabetes mellitus that it would be accepted as a causal condition were it not for the occurrence in a certain number of severe and fatal clinical cases of diabetes of hypertrophy instead of atrophy of the islands. Analysis of the reported cases of diabetes in which the condition of the islands of Langerhans were carefully noted shows that it is in the diabetes of the young especially that the hypertrophied state of the islands is encountered, and the suggestion is a strong one and merits careful consideration whether the islands in these cases may not have been imperfectly developed and have yielded a secretion of such altered and abnormal quality as to have been the cause of the disturbance of the carbohydrate metabolism leading to the fatal diabetes. The conception is unusual, but it is not impossible and is in harmony with the facts so far collected. The mere fact that the pancreas and the islands of Langerhans as a whole are so rarely found even apparently normal in diabetics must be accepted as of great significance in respect to the point as to whether, after all, alterations in the islands are more than accidentally connected with the disease; for our histological methods are still so far from perfect that subtile cellular changes, now only suspected, will surely be discovered in the future.

In comparison with the great advances already achieved in the infectious diseases stands the relatively small progress made in the clearing up of the etiology of the more chronic diseases of the important viscera. The problems of the latter have, until now, except here and there, resisted all effort at their solution. What is chiefly lacking to a fresh and successful endeavor is a suitable and promising method of investigation, and we may well welcome, therefore, an experimental one which aims at a study of important tissues and organs transferred from one animal to another of the same or even of a different species, and the gradual ablation or sudden increase of important organs in order to establish the influences exerted by a new environment on certain organs, or transplanted organs on a new host, or the limit of destruction of tissues with normal and with pathological reactions, or the manner and degree of control capable of being exercised over a greatly augmented activity of different organs. The technical surgical operation involved in this kind of experimentation, on account of the necessity of maintaining unimpaired the circulation of the blood, is great but not impossible of achievement; and the final goal is so important, involving as it does the possibility of substituting sound for diseased organs in human beings, that no effort will or should be spared to reach it.

This method of experiment has, of course, nothing in common with the older one of transplanting minute portions of tissue from one animal to another. In spite of survival of these grafts, for a time, they have yielded very little of an active functioning nature to the new host. By the method of preservation of the circulation through the transplanted organs their

functions are maintained and, as a rule, in a perfect manner. Hence it now becomes possible to place sensitive and important viscera under new experimental conditions which may aim to resemble or to reproduce those believed to give rise to common pathological states in man, and to observe the effects over a long period of time. This method, in the hands of Carrel, its chief exponent, has already produced many new and highly important results relating to the blood-vessels, the kidneys, thyroid gland and other organs. It is a matter of no small theoretical and practical significance that arteries can be transplanted successfully from dog to cat, and *vice versa*, and from man to dog, and that keeping extirpated arteries under sterile conditions at refrigerator temperature for twenty or thirty days, or even longer, does not interfere with the results of transplantation; and the histological changes suffered by the transplanted vessels, whether in the same or different species, or made immediately after removal from the body or after several weeks in cold storage, are small in conformity with their perfect function as blood vessels.

The knowledge of the processes of inflammation has already been, and medical and surgical practise may hope to be, assisted by studies of the leucocytes from a physiologico-chemical point of view. The indispensable phagocytic function of the leucocytes—whether directed against micro-parasites or somatic cells worn out by physiological use or destroyed by pathological effects—is now so generally admitted that it seems trite merely to mention the property. But this *living* function of the leucocytes is supplemented by their demonstrated power to yield upon dissolution active proteolytic enzymes of considerable potency capable of attacking native and alien proteid. This enzymotic action can be and often is held in check by certain antienzymes contained normally in the plasma of the blood. Opie, to whom we owe the discovery of the antienzymotic power of the blood-serum, has shown, also, how greatly the issue of an inflammation is affected by the balance between the leucocytes and the serum, and how a purulent inflammation with solution of tissue is the product of collections of leucocytes whose enzymotic power is unrestrained by serum, and that the more superficial and less destructive sero-purulent exudations have the potential enzymotic activity of the leucocytes balanced and checked by the serum. It would appear not to be a long or particularly difficult step from the establishment of these conditions by experiments on animals to their application in human beings in whom the issue of inflammations may be promoted in the direction offering the best hope for the patient.

Until recently, all progress regarding tumors, excepting in their histological structure and place of origin, has been in respect to their surgical treatment. Improvement in operative methods by which local infection of the site of operation and general dissemination of tumor cells have been avoided, and the more complete removal of all tumor-infected tissue accomplished, have increased greatly the number of cures of malignant tumors. We are still ignorant of the cause of tumors, and there is no likelihood that the ignorance will soon be dispelled. But the study of transplantable tumors in mice and rats, chiefly, has already yielded many important facts concerning the biological conditions underlying tumor growth. These small animals, the domesticated races especially, are not infrequently the subject of spontaneous tumors which compass their death. The tumors are, therefore, malignant; in mice they are carcinomata, chiefly, springing from the mammary glands; in rats, sarcomata, chiefly, taking origin from

more diverse organs. Many, although not all, of the tumors are transplantable to new individuals of the same species and race, never to animals of another species, and less often to those of another race of a given species.

There is something extremely subtile in the conditions underlying successful transplantation within one race since it may be determined by such minor factors as environment and mere quality of food. A tumor used to growing in Danish white mice may fail utterly to grow in Berlin white mice, and one used to growing in Berlin mice and unable to grow in Norwegian mice, may lose its capacity to grow in Berlin mice transported to Christiania and kept there for a period before inoculation.

Artificial selection of fast-growing strains can modify a slowly-growing into a rapidly-growing tumor and increase the percentage of successful implantations. Once a high degree of power of growth is secured, it can be maintained. The method of selection for virulence is analogous to that for securing virulent strains of bacteria. But the analogy does not go much farther. It may be set down as a rule to which at present the exceptions are insignificant, that the more virulent a tumor is, the less it tends to produce secondary growths at a distance from the primary nodule. Tumors which grow slowly cause, not very infrequently, large secondary growths especially in the lungs; but those which grow rapidly never. Moreover, once the original graft of tumor has begun to grow vigorously, it is almost impossible to implant successfully a second graft. The metastases originate from tumor cells which have entered the circulation and been deposited in the capillaries of the lung. Now, highly virulent tumors, as is to be expected, invade the blood-vessels just as the less virulent tumors do, but in one case the cells at a distance develop into new tumors and in the other they lie dormant. If such a distinction exists in human beings, the subjects of malignant tumors, it has not been made out; but there are great variations in metastases in human cases of tumors, which have never been brought under any law governing tumor growth. My purpose, therefore, in speaking of this peculiar feature of tumor growth in mice is to bring out the fact of the existence of a form of immunity to tumor cells which may be restricted to one part of the body, or be general to the whole body. This immunity Ehrlich called *atrepsy* and he conceives it to be an expression of deprivation of the peculiar foodstuff required for tumor growth. In any body this peculiar nutriment is limited in quantity and hence if cells very highly avid with reference to it are growing actively in any part of the body they may draw all that is available to them and leave none for cells, even of the same nature, which are less avid or away from the focus of its accumulation. The immunities of species, possibly of races also, and the more subtile forms of immunity alluded to, Ehrlich thinks may be atreptic; and for this view there is more or less foundation in facts developed by experiment.

There remain many features of the experimental study of tumors of absorbing interest to the student of tumors in human beings, but they can not be discussed here without extending widely the length of this address. I may, perhaps, allude, before passing to another and quite different topic, to the interesting fact of the occurrence of grades of acquired active immunity in rats and mice that have been inoculated with tumor grafts which have grown but slightly, or which, having grown to a considerable size, later undergo complete absorption. Mice and rats which have recovered spontaneously from tumors

can be reinfected with new and more virulent grafts with difficulty or not at all; and recently the interesting fact has been discovered in Ehrlich's laboratory that in such partially immune mice a tumor which was originally adeno-carcinoma tends to revert to adenoma, or from a more heterogeneous to a more homogeneous structure. We see in this observation how fundamentally the state of the host reacts upon the nature of the tumor, just as in the case of increased virulence we saw how greatly the state of the tumor cells reacted on the host. And we can see the operation of this reciprocal interaction of tumor and host in the fundamentally important transformations in types of tumor, from cancer to sarcoma as shown by Ehrlich and Leo Loeb, and from sarcoma to adeno-carcinoma as observed by Jobling and myself, which are part of the recent gains accruing from the experimental study of tumors. Then I might add a word on the outlook for a more efficient therapeutics of tumors, now that tests can be made upon animals under conditions of scientific accuracy of experiment which will permit of the results being interpreted in a strict rather than in an empirical manner. Just as long as every therapeutic advance had to be made upon and with human beings the victims of tumors, just so long was it impossible to approach the subject in a truly scientific way, for just so long was it impossible to secure that control of experimental conditions that alone can make biological experiment accurate and advance logical and not a thing of chance.

I will now ask you to turn with me to a brief discussion of certain topics in bacteriology which are compelling attention at present. Bacteriology in relation to medicine suffered from a period of reaction to its many brilliant achievements and had for a time lingered somewhat in too familiar fields. But new problems, the direct outgrowth of the old acquisitions, are opening up and new lines of work are being laid down, some of which are of such gigantic importance to the larger interests of social hygiene, that many new forces are being brought into operation.

Perhaps the chief single compelling phenomenon is that of the microbe-carrier, who is everywhere coming to be regarded as a serious menace to the health of communities. He is not a new discovery, for, as regards diphtheria, he has been known for more than a decade. But now he has been found to disseminate typhoid fever, dysentery, plague, cholera, influenza, spinal meningitis, and in certain localities a host of protozoan diseases. Moreover, he is not, like the victim of tuberculosis, who is also a microbe-carrier, a sufferer from the disease which he disseminates; he is, as a rule, immune to the microbes in an actual sense and is usually ignorant of the sinister rôle which he plays in life. The period of time during which these pathogenic microbes can exist in the body is very variable, but may be great. In the case of typhoid fever forty-two years have been known to have elapsed since the attack, at the end of which time typhoid bacilli were still being eliminated with the dejecta. Plague bacilli have been present in the sputum seventy-six days after recovery from plague-pneumonia; influenza bacilli have been found in the sputum one year after an attack of influenza; and still other examples of long persistence of pathogenic microbes could be cited.

What is remarkable is that this persistence of pathogenic germs in the body can not be explained on the supposition that they are really outside the body, residing on mucous membranes, and hence not subject to the ordinary forces of destruction which operate in the blood and tissues. The typhoid bacillus increases chiefly in the gall bladder, which is indeed not within

the body, strictly speaking; but foci of development may exist in the kidney for many months, infecting the urinary bladder, and in bone and muscle, and they are strictly within the body. A distinction is not readily made between capacity of growth within and on the surface of the body, but evidence exists tending to show that certain tissues may develop immunity to pathogenic bacteria which usually injure them, and certain bacteria develop capacity to survive under conditions which are usually fatal to them.

It is just in this connection that we are learning that bacteriolysis and bactericidal effects do not necessarily go along with spontaneous recovery from and acquired immunity to bacterial diseases. These forces of immunity may be in active operation, so far as tests made outside the body with the blood indicate, at a time that the very bacteria from and against which they have developed may still be surviving in the body. Typhoid bacilli have been cultivated from the blood long after the subsidence of symptoms of typhoid fever and at a time when the titre of serum bacteriolysis was of prodigious height; pneumococci have been detected in the circulating blood of animals actively immunized to the pneumococcus; anthrax bacilli have been grown from the blood of immune and healthy sheep protected by anthrax vaccine, and living virulent tubercle bacilli of the human type have been obtained from the healthy lymphatic glands of calves inoculated with Bovo-vaccine and in consequence already immune to bovine tuberculosis. It is clear, therefore, that the immune state, so far as bacteria are concerned, can be no one-sided phenomenon in which the fact of all importance is the condition of the host, and that of small importance the condition of the invading bacterium. The phenomenon is, indeed, a reciprocal one and must take account of a high degree of capacity for adaptive changes on the part of the parasite as well as on the part of the host.

Many of the diseases due to protozoa show in a more striking way the same facts of mutual adaptation of parasite to host; and this power of survival of the parasites in the healthy body is what makes suppression of diseases transmitted from host to host by blood-sucking insects a matter of such difficult and uncertain achievement. The fact as regards malaria is well known, and this paradoxical condition of immunity and infection is established as true for trypanosomic, piroplasmic and spirillar diseases of man and animals. Koch has drawn attention, in a recent report, to the existence in the blood of healthy natives of the trypanosoma of sleeping-sickness from which the Glossina may readily become infected and made able to carry the disease. It is clear that the future studies in immunity will take into more direct account the changes in the infecting parasite produced by the immune state, and will seek means of their suppression which will leave the host uninjured and weaponed for a more successful resistance to invasion. In this field prediction is hazardous; but it need not excite great surprise if this desideratum should be accomplished through specific drugs suited to the purpose by subtile molecular adaptations, rather than by sera prepared by immunization with the parasites themselves.

The long discussion of the part played in natural and acquired immunity by the blood plasma or serum and the mobile phagocytes has now been settled so as to include both factors. The body fluids and the blood serum chiefly carry, as a result of immunization, dissolved substances which act at one time by neutralizing toxines that are themselves injurious and at another in sensitizing bacteria and other corpuscular bodies so that they may be en-

gulfed by phagocytes which destroy and render them innocuous. The discovery of the opsonins in the normal blood and their increase in states of induced immunity to bacterial and other infections, has added greatly to the clearing up of some of the complicated phenomena of the immune state. That many virulent bacteria—anthrax, chicken cholera, pyocyaneus, staphylococci and streptococci, pneumococci and others—exhibit negative chemotoxis, or are ingested far less by phagocytes than avirulent strains of the same microorganisms, is an old observation, and it is very enlightening to find, as Rosenow has, that virulent strains of pneumococci do not bind opsonin, while avirulent strains do, and extracts prepared from the virulent germs protect avirulent ones from phagocytosis to a greater degree than extracts of the avirulent pneumococci themselves. Cultivation outside the body as saprophytes of parasitic and non-phagocytable pneumococci and other bacteria, tends to alter their relation to the opsonins and to phagocytosis. From which it appears that virulence and negative chemotoxis depend upon certain chemical states of bacteria, determined by the conditions of their existence, and affecting the nature of their metabolic products, among which last are substances that are antagonistic to the functioning of the opsonins. Far as we still are from a clear and full conception of the distinction between virulence and avirulence in bacteria, we must nevertheless welcome this concrete fact as in itself a great gain.

The body infected with bacteria or other pathogenic microorganisms, although it survive the infection, may not be rendered more resistant; it may be rendered more susceptible to reinfection—that is, it may be sensitized to the infecting agent or its poisonous products. The state of hypersensibility, or anaphalaxis, the converse of that of immunity, has been studied with energy and profit during the last two years. Perhaps the best known example is the abnormal reaction developed when an animal infected with tubercle bacilli is injected with the products of the growth of the bacillus. Blood serum contains a substance, or substances, which under suitable conditions develop a reaction of this character. That the human organism reacts more vigorously to second and subsequent injections of horse serum than to the first injection is shown by the reports of many instances in which these stronger effects were noted after administering diphtheria antitoxin. It appears that the reaction of hypersensibility depends for its expression upon the existence in the sensitized body of a substance of the nature of an antibody comparable to, but doubtless differing widely from, the antibodies which are developed during the process of immunization proper to bacterial and other cells. In the case of hypersensitiveness to serum a second injection, in such small animals as the guinea-pig, may result fatally in a few minutes or after several hours; but should it not so result, the animals have been robbed of their sensitive or anaphalactic state and been rendered "immune" to horse serum in the usual sense, or antianaphalactic. These superficial facts suffice, in a way, to indicate that the antibodies governing the anaphalactic state differ from those governing the immune state, and it is, therefore, interesting to learn that they differ further in failing to give the Bordet-Gengou reaction of complement-deviation.

Studies in immunity pursued during the past several years have tended to show that it may be general to the body or more marked in one part than in another. Hence we have to distinguish a state of "general" and a state of "local" immunity; and it would appear, also, that the whole body may be sensitized or that sensitization may

be more limited in extent and restricted to certain tissues or locations. Wassermann succeeded in affecting the endothelial cells of the pleura by direct pleural inoculation of typhoid bacilli so as to increase their power to produce antibodies above that of the other tissues of the body, and Noguchi succeeded by localizing a tetanus infection in the subcutaneous tissue of the thigh to make it impossible for tetanus toxin to enter the body from that location while all other avenues of entry were left unaffected. And, as a parallel to these states of immunity, we see in the phenomenon of Arthus that the subcutaneous tissues of the rabbit can by repeated injections of horse serum be sensitized and thus made to react with a degree of vigor and inflammation which may cause their destruction, the rest of the body meanwhile showing no increase of sensitiveness.

The hypersensitiveness of the tubercular state would appear to be localized in tissues far removed from the seat of the infecting tubercle bacilli, and probably every part of the tuberculous organism is in a potential hypersensitive condition. In any case, the ophthalmo-reaction of Calmette and the cuti-reaction of v. Pirquet, both of which are yielding good service in the diagnosis of tuberculosis and taking the place of the more serious general reaction of hypersensitiveness following upon tuberculin injection, show that in the conjunctiva and the skin the cells are sensitized and react rapidly and in a characteristic manner to tuberculinization.

It will be clear to you that in following the diverse reactions of the body to foreign substances, among which parasitic microorganisms play in pathology the chief part, there is gradually being discovered a wide range of phenomena, some desirable and beneficial, some objectionable and injurious, which together constitute the effects of natural disease or of efforts to thwart and overcome it. It will become the particular quest of the immediate future to attempt the unraveling of those biological conditions which underlie one or the other of these, and to secure to the use of medical practise those effects which may be beneficial and to remove from it those which are injurious. Were there still time at hand, I should present to you certain newer facts in protective inoculation with bacteria and of serum therapy which are not without good augury for preventing certain infective diseases of man and animals, and of overcoming them by specific serum therapy once they have developed. And then I should try to interest you in the remarkable progress which has been made, and is being made almost daily, in the discoveries in specific chemical therapeutics which make the control of certain protozoan diseases—trypanosomiases and spirilloses especially—very hopeful for the future. I must, however, not detain you longer from the enjoyment of the interesting scientific program which has been prepared for this hour.

SIMON FLEXNER

CHARLES A. YOUNG

THE past five months have brought severe losses to astronomy in the deaths of five of its distinguished men: in Germany, Vogel, of Potsdam; in France, Loewy, of Paris, and Janssen, of Meudon; in this country, Asaph Hall; and now Charles A. Young, who died at Hanover, N. H., on January 3.

There is some consolation, however, in the fact that all of these men had reached advanced years,[1] and had in a measure rounded out their scientific careers, although the three first named were still in active service as directors of large observatories.

Charles Augustus Young was born on

[1] Average age, 75 years.